Applicants submit that the declaration as filed is correct, even though all of the inventors listed at the time the application was filed are not listed. Under M.P.E.P. § 201.03:

> Where the first-filed executed oath or declaration was filed on or after December 1, 1997 and sets forth an inventive entity which is different from the inventive entity initially set forth at the time of filing of the application, the actual inventorship of the application will be taken from the executed oath or declaration.

The purpose of this rule is to avoid the possibility of an error in inventorship. The declaration as submitted on October 26, 2000, correctly names the actual inventive entity, Peizhi Luo, of the pending application. Accordingly, Applicants respectfully request withdrawal of the objection.

Specification

The application is objected to because is does not contain as abstract as required by 37 C.F.R. § 1.72(b). An abstract has been prepared for the pending application and is submitted on a separate sheet of paper. Accordingly, Applicants request withdrawal of the application.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 11-18 are rejected under 35 U.S.C. § 112, second paragraph for being indefinite. Specifically, independent claim 11 is objected to for failing to define the term "signaling". Claim 11 has been amended to clarify what the term signaling refers to as supported by the specification on page 46, lines 17-30. Accordingly, Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 102(e)

Claims 1-4, 6-9 and 11-19 are rejected under 35 U.S.C. § 102(e) as being anticipated by Stahl, et al. U.S. Patent No. 5,844,099.

Stahl et al. teach method of making antagonists to any cytokine that utilizes an α specificity determining component (i.e. sRα) which when combined with a cytokine binds to a first β signal transducing component (β1) to form a nonfunctional intermediate which then binds to a second β signal transducing component causing β receptor dimerization and consequent signal transduction. That is, Stahl et al., teach methods of making chimeric heterodimers having the composition sRα:β1, that act as cytokine antagonists by binding the cytokine to form a nonfunctional complex; see column 6, lines 20-32. In addition, targeted mutagenesis can be used to generate additional candidates to test for antagonistic properties.

In contrast, the present invention utilizes a computational modeling system that allows the generation of extremely stable proteins without necessarily disturbing the biological function of the protein itself. Generally speaking, this is done as follows. A three dimensional structure of a protein is input. Each residue position may be classified as a surface, boundary or core residue, and the residue positions are classified as either fixed or variable. For each variable position, a set of amino acid side chain rotamers are chosen, with at least one variable residue position having rotamers from at least two different amino acid side chains. The calculation then proceeds as follows: for each variable position, the energy of interaction of each rotamer with both the template (e.g. anything that is fixed, including the backbone and any fixed residues) and all possible rotamers at all variable positions is calculated. This is done using any number of

different scoring functions. The calculation of the energy of interaction is facilitated by the use of Dead End Elimination (DEE). DEE is used to decrease the number of required calculations by eliminating rotamers that cannot be part of the global minimum; that is, by throwing out "bad" rotamers, the number of rotamers that needs to be analyzed decreases, and the global minimum solution is found more quickly. Once the global minimum is reached, local minima can be found by using additional analysis, such as a Monte Carlo analysis, which makes random changes and then recalculates the energy of interaction.

As can be seen from the foregoing discussion, the computational method of the present invention is used to generate analogs of naturally occurring cell surface receptors and ligands which can then be screened for the desired activity. Basically, any receptor/ligand pair can be chosen. The receptor is then modeled in an active conformation to create a structural mimic of the active, naturally occurring receptor. These receptors can then be used in a variety of screening assays to identify ligand analogs capable of modulating the biological activity of the receptor. Thus, the present invention teaches a generic method for making variant receptor/ligand pairs that retain the biological properties of wild-type receptor/ligand pairs.

An anticipation rejection requires that a single reference expressly or inherently disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); MPEP § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)). Additionally, the reference must enable and describe the claimed invention "sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." 31 USPQ2d at 1673. To be enabling, the reference must teach

the skilled artisan how to make and use the full scope of the claimed invention without undue experimentation. *See Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997).

As stated above, the present invention uses a computationally modeling system, PDA, to design variants of receptor/ligand pairs. Moreover, the present invention does not rely on experimentally synthesizing chimeric heterodimers of the extracellular domain of sRα:β1 to function as antagonists of the CNTF family of cytokines. Accordingly, it is clear that Meyer et al. do not disclose or suggest a method for generating antagonists of cytokines using computational design methods. Applicants respectfully request withdrawal of the rejection.

Claims 1-4, 6-12 and 17-19 are rejected under 35 U.S.C. § 102(e) as being anticipated by Jin et al., U.S. Patent No. 6,093,547.

Jin et al. teach a method of identifying and cloning a novel cell surface morphogen receptor based on the "cross talk" among cell surface receptor molecules species variants. The method described by Jin et al. consists of using the *Drosophila* genome as the starting material, from which candidate receptor molecules are isolated using PCR DNA amplification. Potential candidate receptors in *Drosophila* are identified based on cell receptors identified in other species. Moreover, the receptor molecules are limited to cell surface molecules that share less than 26% identity with the extracellular domains of other, known receptor molecules whose ligands are members of the TFG-β superfamily. See column 9, lines 19-60.

In contrast, as outlined above, the present invention uses a computational modeling system to identify variants of existing receptor/ligand pairs. Thus, the present invention teaches a generic method for making and using receptor/ligand pairs, as opposed to a method tailored to the specific identification and isolation of a subclass of cell receptors, i.e., morphogens. Thus, it is clear that Jin et al. do not disclose or suggest a method for generating receptor/ligand variants using computational design methods. Applicants respectfully request withdrawal of the rejection.

Claims 1-4, 6-12, 18 and 19 are rejected under 35 U.S.C. § 102(e) as bing anticipated by Ichijo et al., U.S. Patent No. 5,968,752.

Ichijo et al., teach a method for identifying OP-1 analogs using affinity binding screens. Moreover, the screening techniques taught by Ichijo are well known in the art. Thus the method taught by Ichijo is limited to the identification of OP-1 analogs that bind the ALK-1 receptor. See Column 8, line 66 through column 9, line 34; Example 4.

As reiterated above, the present invention uses a computational modeling system to identify variants of existing receptor/ligand pairs. Thus, the present invention teaches a generic method for making and using receptor/ligand pairs, as opposed to a method tailored to the specific identification and isolation of ligands that have specific affinity for the ALK-1 receptor. Thus, it is clear that Ichijo et al. do not disclose or suggest a method for generating receptor/ligand variants using computational design methods. Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 103(a)

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Stahl et al., Jin et al., and Ichijo et al as applied to claims 1-4 and 6-19 above and further in view of Ochoa et al.

The teachings of Stahl, Jin, and Ichijo have been summarized above.

Ochoa et al., U.S. Patent No. 5,889,143, teach methods for screening and identifying soluble immunosuppressive factors that can be used to treat diseases of the immune system. The immunosuppressive factor taught by Ochoa, et al. is a polypeptide formed by the degradation of the p50 member of the NF-κB. This factor was isolated from tumor bearing mammals via its effect on TCR related proteins. The method of isolation, i.e., a solid support is well known in the art.

The teachings of the present invention have been summarized above.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met: (1) the prior art must provide one of ordinary skill with a suggestion or motivation to modify or combine the teachings of the references relied upon by the Examiner to arrive at the claimed invention; (2) the prior art must provide one of ordinary skill with a reasonable expectation of success; and (3) the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed invention, as well as the reasonable

expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

The Examiner states that Claims 1-19 are unpatentable over Stahl et al., Jin et al., and Ichijo et al as applied to claims 1-4 and 6-19 above and further in view of Ochoa et al. Applicants disagree because the combined teachings of Stahl, Jin, Ichijo does not teach or suggest each and every limitation of claims 1-19.

Claims 1-19 are disclose methods of screening for ligand analogs to cell surface receptor analogs. The receptor/ligand analogs claimed in the present invention are generated using a computational modeling system. Basically, analogs of any receptor for which a three dimensional structure is available can be generated. Analogs that bind to the receptor analog can then be identified using screening techniques known in the art.

Applicants submit there is no suggestion in any of the references cited by the Examiner to generate receptor analogs using computational modeling. Moreover, the methods disclosed in the cited references are limited to specific cell surface receptors that are identified using recombinant DNA technology.

Furthermore, a person of skill in the art would have no reasonable expectation of success for generating the receptor/ligand pairs of the present invention using the methods described in Stahl, et al., Jin et al., Ichijo et al., and Ochoa et al.

Finally, none of the references teach every limitation of claims 1-19. Specifically, none of the references teach methods of generating receptor analogs using computer

modeling which are then used to identify ligands. Accordingly, applicants request withdrawal of the rejection.

Attached hereto is a marked-up version of the changes made to the claims by the "Restriction and Amendment". The attached page is captioned **"Version with markings to show changes made."**

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 7/31/01

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

In the Claims:

Claim 11 was amended as follows:

11. (Amended) A method of screening for ligand analogs, said method comprising the steps of:

a) providing a eukaryotic cell, comprising a non-naturally occurring cell surface receptor analog comprising an amino acid sequence that is less than about 95% identical to the extracellular domain of a corresponding naturally occurring human cell surface receptor, wherein said receptor analog binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor;

b) adding a candidate ligand to said eukaryotic cell; and

c) determining if said candidate ligand modulates the signaling activity of said cell surface receptor analog.

Appendix of Pending Claims

1. A method of screening for a ligand analog, said method comprising the steps of:
   a) adding a candidate ligand to a non-naturally occurring cell surface receptor analog comprising an amino acid sequence that is less than about 95% identical to the extracellular domain of a corresponding naturally occurring human cell surface receptor, wherein said receptor analog binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor; and
   b) determining the binding of said candidate ligand to said receptor analog.

2. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a eukaryotic cell.

3. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a prokaryotic cell.

4. A method according to claim 1, wherein said cell surface receptor analog is on the surface of a virus.

5. A method according to claim 1, wherein said cell surface receptor analog is immobilized on a solid support.

6. A method according to claim 1, wherein said cell surface receptor analog is in an aqueous solution.

7. A method according to claim 1, wherein said cell surface receptor analog comprises only an extracellular domain.

8. A method according to claim 1, wherein said cell surface receptor analog comprises an extracellular domain and a transmembrane domain.

9. A method according to claim 1, wherein said cell surface receptor analog comprises an extracellular domain, a transmembrane domain and a cytoplasmic domain.

10. A method according to claim 1, further comprising the steps of:
   c) designing said cell surface receptor analog, wherein said step of designing is executed by a computer program and wherein said cell surface receptor analog has a calculated structure that is different from a calculated structure of said corresponding naturally occurring human cell surface receptor;
   d) synthesizing a nucleic acid encoding said cell surface receptor analog; and

e) expressing said cell surface receptor analog.

11. (Amended) A method of screening for ligand analogs, said method comprising the steps of:

a) providing a eukaryotic cell, comprising a non-naturally occurring cell surface receptor analog comprising an amino acid sequence that is less than about 95% identical to the extracellular domain of a corresponding naturally occurring human cell surface receptor, wherein said receptor analog binds a natural ligand for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor;
b) adding a candidate ligand to said eukaryotic cell; and
c) determining <u>if said candidate ligand modulates</u> the signaling <u>activity</u> of said cell surface receptor analog.

12. A method according to claim 11, wherein said cell surface receptor analog is a chimeric receptor comprising an extracellular domain and a cytoplasmic domain from at least two different naturally occurring cell surface receptors.

13. A method according to claim 1 or 11, wherein said cell surface receptor analog comprises an exogenous dimerization domain.

14. A method according to claim 13, wherein said exogenous dimerization domain is fused to the cytoplasmic domain of said cell surface receptor analog.

15. A method according to claim 13, wherein said exogenous dimerization domain is fused to an internal site of said cell surface receptor analog.

16. A method according to claim 13, wherein said exogenous dimerization domain is fused to the extracellular domain of said cell surface receptor analog.

17. A method according to claim 1 or 11, wherein said naturally occurring human cell surface receptor is a cytokine receptor.

18. A method according to claim 1 or 11, wherein two monomers of said naturally occurring human cell surface receptor are crosslinked, whereby said non-naturally occurring cell surface receptor analog is formed.

19. A recombinant chimeric cell surface receptor complex, comprising at least two different monomers of a non-naturally occurring cell surface receptor analog wherein each of said monomers comprises an amino acid sequence that is different from an amino acid sequence of a corresponding naturally occurring human cell surface receptor, and wherein said recombinant chimeric cell surface receptor complex binds a natural ligand

for said naturally occurring human cell surface receptor at the same or higher binding affinity than said naturally occurring human cell surface receptor.